Comparison of Effect of Meperidine Versus Fentanyl as an Adjuvant to Epidural Bupivacaine on Duration of Labor: A Randomized Controlled Study

Masoomeh Nataj Majd[1], Maryam Farid Mojtahedi[2], Arman Taheri[3], Mehdi Sanatkar[4], Nader Ali Nazemian Yazdi[5]

[1] Department of Anesthesiology, Arash Women's Hospital, Tehran University of Medical Sciences, Tehran, Iran

[2] Department of Obstetrics and Gynecology, Arash Women's Hospital, Tehran University of Medical Sciences, Tehran, Iran

[3] Department of Anesthesiology and Pain, Imam Khomeini Medical Center, Tehran University of Medical Sciences, Tehran, Iran

[4] Department of Anesthesiology and Pain, Farabi Hospital, Tehran University of Medical Sciences, Tehran, Iran

[5] Department of Anesthesiology, Amir A'lam Hospital, Tehran University of Medical Sciences, Tehran, Iran

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Abstract- Epidural analgesia (EA) is one of the best pain relief for many pregnant women in labor. This study was conducted to evaluate the effect of epidural analgesia provided by a combination of bupivacaine plus meperidine or fentanyl on the mother, fetus, and labor process in term nulliparous women. A total of 558 nulliparous women were randomized into two groups of 279 subjects. The BF (Bupivacaine-Fentanyl) group received 16 ml bupivacaine 0.125% plus 50 mg fentanyl as a loading dose; then, an intermittent bolus of the same solution was administered once the patient requested analgesia. The BM (Bupivacaine-Meperidine) group received a loading dose of 16 ml bupivacaine 0.125% plus 20 mg meperidine followed by an intermittent bolus of the same solution if the patient requested analgesia. The time of labor phases 1 and 2 and the incidence of side effects were recorded. After the intervention, the pain score was significantly lower in the meperidine group compared to the fentanyl group during labor (P=0.006). The duration of the active phase of labor (P=0.04) and the rate of cesarean section (P=0.01) were significantly higher in the fentanyl group compared to the meperidine group. The duration of the second stage of labor was not significantly different between the two groups (P=0.24). Apgar score was significantly higher in the meperidine group. This study found that epidural meperidine could be a suitable alternative to fentanyl for improving pain relief and shortening the active phase of delivery without increasing the risk of the neonatal low Apgar score.

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Keywords: Epidural analgesia; Meperidine; Labor duration

Introduction

The availability of an effective and safe method for analgesia during labor has always been considered by physicians. Epidural analgesia (EA) is a popular and effective strategy for pain relief during labor; however, in spite of its efficacy and widespread use, there has been significant controversy regarding its impact on labor outcomes, and it is controversial whether EA prolongs labor. A number of meta-analysis studies have shown that EA prolongs labor, although only modestly. It has been confirmed that EA prolongs the first and second stages of labor by 42 and 14 minutes, respectively, but the clinical relationship is unclear (1). The definition of the prolonged second stage in pregnant women who have underwent regional analgesia has been revised by the American College of Obstetricians and Gynecologists (i.e., >3 h for primigravid and >2 h for multigravida women) (1). Since increase duration of labor may lead to maternal and neonatal events, some studies have investigated the effects of different epidural regimes on the outcome of labor (2-4). One previous study showed the mode of delivery with different epidural local anesthetics with regard to obstetric outcomes but found no difference between the groups (4). Hence, this study was done to assess the effect of a combination of two drugs (a local

Corresponding Author: N.A. Nazemian Yazdi
Department of Anesthesiology, Amir A'lam Hospital, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 2166703819, Fax: +98 2166704805, E-mail address: nnazemian@sina.tums.ac.ir

anesthetic and an opioid) on accelerating labor. Meperidine is routinely used as an adjuvant drug for epidural anesthesia in some operations. It is a safe drug for route epidural administration (5,6). In labor, meperidine is also one of the most frequently used opiate agonists. Previous studies have identified that meperidine can decrease the duration of active labor in nulliparous case with term gestational age (7,8). However, previous studies have consistently cast doubt on meperidine effectiveness in reducing maternal labor pain and its effects on the newborn (9,10). In addition to the maternal sedating effects of meperidine, there is also the some risk of maternal delayed gastric emptying, aspiration, and respiratory depression (11). Meperidine affects the duration od labor and significantly shortens the duration of the active phase of labor in nulliparous subjetcs (8). Moreover, it has adverse maternal and neonatal effects. Therefore, the present study was done to examine the effects of epidural meperidine on labor progression and to compare it with fentanyl considering that the administration of opioids via the epidural route has less maternal and neonatal side effects (12).

Materials and Methods

The study was approved by the Investigational Review Board of School of Medicine, Tehran University of Medical Sciences. Informed written consent was obtained from all cases. This study was registered in the Iranian Registry of Clinical Trials (www.irct.ir) with a unique identification number (IRCT20170917036227N1). Five hundred and fifty-eight healthy (ASA I, II), 18-45-year-old term (≥37 weeks) nulliparous women in the active phase of labor that had a preference for EA were enrolled in the study. The primary outcomes were the length of labor and the rate of cesarean section. Secondary outcomes of interest were pain relief, indices of maternal and neonatal well-being, and infant Apgar score. Randomization was applied by random numbers using sealed envelopes. Sealed envelopes indicated the assignment group. The patients were blindly randomized to two groups of subjects. The inclusion process continued until the required number of cases was achieved. The inclusion criteria were term pregnancy (37-42 weeks' gestation), plan for a vaginal birth, a viable single fetus with vertex presentation, no known medical conditions, uncomplicated pregnancy, and age 18-45-year-old. The exclusion criteria were preterm labor (<37 weeks' gestation), administration of meperidine or fentanyl within 24 hours of active labor (regular contractions and cervical dilatation of at least 3 cm and maximum 5 cm), history of pre-eclampsia, severe asthma, history of head trauma, glaucoma, heart or liver complications, diabetes mellitus, pre-existing hypertension, hepatorenal syndrome or another end-organ disease, use of opioid agonist or agonist/antagonist in the past 6 h (or within 1 h if given intravenously), morbid obesity (BMI >40 kg/m2), extremes of height (<140 or >180 cm), coagulation disease, or neurological disorders, spine deformity, and skin infection. During labor, the patients were continuously monitored using electrocardiography and pulse oximetry. Non-invasive blood pressure was measured every 5 minutes for the first 30 minutes and then every 15 min throughout the labor period. The epidural procedure was performed in the sitting position using a Tuohy-Schiff needle (18 G) under full asepsis. The epidural space was identified in the L3-4 interspace at a depth of 5 cm using the loss of air resistance technique to achieve a T10-S5 neural blockade. The test dose of 3 ml lidocaine 1.5% plus epinephrine 1:200,000 was injected. If the test dose turned out negative for intravascular injection (less than 20% raise in maternal heart rate within 20 seconds of test dose) and intrathecal injection (no signs of motor block after 3 minutes), preservative-free isobaric bupivacaine 0.125% was administred for labor analgesia with either meperidine or fentanyl following random allocation. BM group (n=279): 20 mg meperidine (2 cc)+4 ml bupivacaine 0.5%+10 ml normal saline for a total volume of 16 ml. BF group (n=279): 50 mcg fentanyl (1 ml)+4 ml bupivacaine 0.5%+11 ml normal saline for a total volume16 ml. A 20-gauge catheter with closed Tip-3 lateral eyes (MEDIKIT, Gurgaon, India) was easily inserted into the epidural space in the sitting position. Then, 3-4 cm of the catheter was left in the epidural space and taped in place. An automatic blood pressure measurement machine and fetal heart monitor were attached to the patient, and 1000 cc Ringer's lactate solution was administered intravenously. After performing the block, the patient was positioned in the supine position with left uterine displacement. After 15 min, the visual analog scale (VAS) score was recorded every minute for 10 minutes, and the motor block was evaluated every 5 minutes for 30 minutes. If the subject complained of pain (defined as VAS >4), a bolus dose of primary solution (16 ml bupivacaine 0.125% plus 50 mg fentanyl or 20 mg meperidine) was administered. During labor, in case of pain intensity above 4 and patient request, based on the expected time of delivery, an intermittent bolus containing 5-10 ml of the BF group solution was injected via the epidural catheter in both groups.

The hemodynamic status and any adverse effects were recorded at 5, 10, 15, 20, and 30 minutes after the injection of the drugs and then every 30 minutes thereafter for up to 3 hours. Observations continued at 1-hour intervals after 3 hours. Observations were performed by midwives that were blind to the administered drugs. After performing the procedure, the onset of sensory and motor block was assessed by labor pain relief and leg moving. Episodes of side effects such as hypotension (SBP <20% of baseline or SBP <90 mm Hg), bradycardia (Heart rate <50/min), respiratory depression (respiratory rate <10/min) and hypoxia (spo2 <90%) were recorded. Hypotension was managed immediately with 5 mg ephedrine injected intravenously. Bradycardia defined as a reduce of heart rate below 50 beats/min was treated immediately by intravenous injection of 0.5 mg atropine. The fetal heart rate pattern was evaluated using continuous monitoring. After the first 30 minutes, the subjects were allowed to ambulate if fetal heart rate pattern was normal and there was no detectable motor block. The participants were asked to report the start of pain relief immediately. The study concluded whenever a patient asked for rescue analgesic or the baby was delivered. The time of active phase as well as phase 1 and 2, rates of C/S and normal spontaneous delivery (NSD) were recorded and analyzed as the predefined primary outcomes. Apgar scores at one and five minutes were also recorded. After delivery, the catheter was removed and its tip was checked.

Results

A total of 558 women, including 279 women in the fentanyl group and 279 in the meperidine group, were evaluated in this study. The mean (SD) age of the patients was 25.97 (4.90) and 26.08 (14.95) years in the fentanyl and meperidine group, respectively (P=0.9). According to bivariate analysis using an independent t-test, the duration of the active phase of labor was significantly longer in the fentanyl group compared to the meperidine group (P=0.04) after the intervention. However, there was no significant difference in the duration of the second stage of labor between the two groups (Table 1). There was a significant difference in the pain severity during labor between the two groups after the intervention (P=0.00). The pain score was significantly higher in the fentanyl group. The rate of cesarean section was 15.4% in the meperidine group and 23.7% in the fentanyl group. A statistically significant difference was found in the delivery type between the two groups (P=0.01), although there was no significant difference in the cesarean section indications between the two groups (P=0.41) (Table 2). After delivery, Apgar scores at one and five minutes were significantly higher in the meperidine group compared to the fentanyl group (P<0.05) (Table 1). Multivariate analysis using multiple logistic regression was done for adjusting age and parity. The odd ratio (95% CI) of C-section delivery was 1.773 (1.149-2.737) in the fentanyl group compared to the meperidine group (Table 3). Multiple linear regression analysis also showed an association between the type of treatment and duration of labor after adjusting for age (Table 4).

Table 1. Duration of labor, Apgar score, and pain score in study groups

	Fentanyl group Mean (SD)	Meperidine group Mean (SD)	*P*
Duration of active phase	3.47(2.39)	3.08(2.03)	0.04
Duration of second stage of labor	3.389 (0.17)	3.385 (0.17)	0.24
1- minute Apgar score	8.45(1.05)	8.74(0.69)	<0.001
5-minute Apgar score	9.63 (0.88)	9.82 (0.55)	0.003
Pain score	1.16 (0.50)	1.07 (0.29)	0.006

Table 2. Reasons for C-section in study groups

		Fentanyl group Number (%)	Meperidine group Number (%)	*P*
Cesarean section		66(23.7)	43(15.4)	0.014
Reason for C-section	**Failure to progress**	14(21.2)	10 (22.7)	
	Arrest	9(13.6)	10 (22.7)	0.41
	Deceleration	43(65.2)	24 (54.5)	

Table 3. Analysis of relationship between C-section and type of treatment

Independent variable	OR (95%CI)	*P*
Type of treatment	1.77 (1.149-2.73)	0.01
Age	1.01 (0.98-1.03)	<0.001

Table 4. Analysis of relationship between duration of labor and type of treatment

Independent variable	beta coefficient (95% CI)	*P*
Type of treatment	4.20 (3.63-4.77)	<0.001
Age	0.01 (0.003-0.03)	0.31

Discussion

The tendency for new methods to prevent long-term delivery and to prevent the need for cesarean section in gynecological surgery has been considered, because long-term delivery has many side effects for mothers and infants. Since some studies have found that epidural analgesia prolongs labor and increases the risk of side effects (13-15), we decided to find a drug combination to overcome the only weakness of labor epidural analgesia, i.e., prolonged labor, which would put an end to many concerns. Does a combination of meperidine and bupivacaine for epidural analgesia shorten the duration of labor compared to fentanyl and bupivacaine? This question was examined in a community-based tertiary medical center. The results of this study justified that epidural meperidine 20 mg plus bupivacaine shortened the labor duration without affecting the degree of mother and infant's sedation and Apgar score compared to a standardized dosage regimen using epidural fentanyl 50 micrograms and bupivacaine. Furthermore, this study found that epidural analgesia with meperidine reduced the rate of cesarean section compared to fentanyl. Meperidine was selected in this study because it can be used via the spinal and epidural routes (5,16), and a number of studies showed that intramuscular meperidine reduced the duration of active labor in nulliparous cases with a normal pregnancy and term gestational age (8,11). Epidural meperidine has gained popularity among anesthetists in Australia and New Zealand, particularly in obstetrics. However, it is less popular in other parts of the world, especially in the United States (1,17). This study showed a significant difference in the pain severity during labor between the two groups (P=0.006), and the pain score was significantly higher in the fentanyl group. In 1992, Edwards reported that a mixture of meperidine and local anesthetics was more favorable for epidural injection in labor. They showed 9 ml bupivacaine 0.25% and 50 mg meperidine increased the duration of analgesia from 87.5 min to 122.2 min, but it was ineffective on speed of onset or quality of analgesia compared to bupivacaine alone (18). Another study showed that dose of 25 mg meperidine provided similar analgesia compare to doses of 50 mg and higher dose (19). These studies justified that the best combination of meperidine and bupivacaine for bolus doses in labor is 25 mg meperidine and 12.5 mg bupivacaine. However, a lower dose of meperidine (20 mg) and a slightly higher dose of bupivacaine (20 mg) was used in this study, and the results showed that the quality of analgesia was better in the meperidine group, which could be due to its local anesthetic effect. The efficacy of a combination of meperidine and bupivacaine for continuous epidural infusion in labor has not been established. Meperidine is an opioid of intermediate lipophilicity that has local anesthetic activity when administered into the epidural space. It absorbed into the CSF rapidly during 15 min, thus providing analgesia effect without hemodynamic deterioration (5). Meperidine has sympathomimetic activity upon systemic absorption causing an increase in cardiac output and heart rate (20). One of the potential adverse effects of the use of intramuscular meperidine in labor is depression of neonatal respiration (21), and thus it cannot be injected near the end of the first stage or during the second stage of labor because of its respiratory depressant effects on the baby. It also has a neuroexcitatory metabolite called normeperidine (22). Although a few studies have studied the potential for these effects after epidural injection of meperidine, the agent is detectable in both maternal and umbilical cord blood after epidural administration (23), and the same precautionary measures should apply. Because of these concerns, meperidine is not an opioid of choice for labor epidural analgesia. Thus, meperidine was used as an epidural adjuvant only in the first bolus dose at the start of the labor active phase and fentanyl was used as intermittent boluses for further analgesia in subsequent doses to avoid the cumulative effect of meperidine. The neonatal Apgar scores at one and five minutes were

significantly higher in the meperidine group compared to the fentanyl group (P<0.05) in the present study. It is well-known that the chief morbidity of labor epidural analgesia is motor block, might prolong labor duration and increase the probability of cesarean section (24). Prolonged labor has side effects and can increase the rate of cesarean section. In the present study, the rate of cesarean section was higher in the BF group, but prolonged labor was not the only reason, and there were other reasons such as non-reassuring fetal heart rate patterns and full arrest; therefore, it is not possible to conclude that meperidine can diminish the C-section rate. Many previous studies have compared the clinical efficacy of various epidural drugs on labor outcome. Some authors evaluated the clinical impact on the labor course of analgesia duration with equivalent doses of ropivacaine and bupivacaine with or without opioids (2,25,26). Some other studies addressed the difference between the effects of epidural ropivacaine and bupivacaine on sensory and motor block using VPS (a 100-mm visual analog pain score) and modified Bromage score (modified Bromage score (BS): BS0, full flexion of hip, knee and ankle; BS1, impaired hip flexion; BS2, impaired hip and knee flexion; BS3, inability to flex hip, knee or ankle; BS3, complete motor block) (9,11,27). Nevertheless, no study has simultaneously compared the labor duration time and C-section rate in nulliparous women using intermittent bolus epidural formulas with fentanyl or meperidine as an adjuvant to bupivacaine. Therefore, we prospectively studied the differences between these two types of epidural labor analgesia regimes and found that the duration of the active phase of labor was significantly longer in the fentanyl group compared to the meperidine group (P=0.04), although there was no significant difference in the duration of the second stage of labor between the two group. Further studies are recommended using other doses of meperidine in addition to other local anesthetics like ropivacaine (28-30). In conclusion This prospective study showed that epidural meperidine was be a suitable alternative to fentanyl for improving pain relief and shortening the active phase of delivery without increasing the risk of low Apgar score.

References

1. Onuoha OC. Epidural Analgesia for Labor: Continuous Infusion Versus Programmed Intermittent Bolus. Anesthesiol Clin 2017;35:1-14.
2. Polley LS, Columb MO, Naughton NN, Wagner DS, Dorantes DM, van de Ven CJ. Effect of intravenous versus epidural fentanyl on the minimum local analgesic concentration of epidural bupivacaine in labor. Anesthesiology 2000;93:122-8.
3. Lacassie HJ, Columb MO, Lacassie HP, Lantadilla RA. The relative motor blocking potencies of epidural bupivacaine and ropivacaine in labor. Anesth Analg 2002;95:204-8.
4. Chen SY, Lin PL, Yang YH, Yang YM, Lee CN, Fan SZ, et al. The effects of different epidural analgesia formulas on labor and mode of delivery in nulliparous women. Taiwan J Obstet Gynecol 2014;53:8-11.
5. Yousef AA, Atef AM, Awais WM. Comparison of fentanyl versus meperidine as supplements to epidural clonidine-bupivacaine in patients with lower limb orthopedic surgery under combined spinal epidural anesthesia. BMC Anesthesiol 2015;15:146.
6. Bujedo BM, Santos SG, Azpiazu AU. A review of epidural and intrathecal opioids used in the management of postoperative pain. J Opioid Manag 2012;8:177-92.
7. Nunes RR, Colares PGB, Montenegro JP. Is pethidine safe during labor? Systematic Review. Rev Bras Ginecol Obstet 2017;39:686-91.
8. Sadrossadat H, Ahangari A, Marashi S, Yaghooti AA. Delirium and Pain after Strabismus Surgery in Children Undergo General Anesthesia: A Comparison of Paracetamol and Meperidine. Arch Anesth Crit Care 2017;3:308-312.
9. Bricker L, Lavender T. Parenteral opioids for labor pain relief: a systematic review. Am J Obstet Gynecol 2002;186:S94-109.
10. Smith LA, Burns E, Cuthbert A. Parenteral opioids for maternal pain management in labour. Cochrane Database Syst Rev 2018;2018:CD007396.
11. Shariat Moharari R, Hadavi M, Pourfakhr P, Najafi A, Etezadi F, Khajavi MR. Evaluation of the Postoperative Analgesic Efficacy of Intraperitoneal Ketamine Compared with Bupivacaine in Laparoscopic Cholecystectomy. Arch Anesth Crit Care 2016;2:146-9.
12. Privado MS, Sakata RK, Issy AM, Garcia J. Comparative study of epidural and intravenous fentanyl for postoperative analgesia of orthopedic surgeries. Rev Bras Anestesiol 2004;54:634-9.
13. Hasegawa J, Farina A, Turchi G, Hasegawa Y, Zanello M, Baroncini S. Effects of epidural analgesia on labor length, instrumental delivery, and neonatal short-term outcome. J Anesth 2013;27:43-7.
14. Zhang J, Landy HJ, Branch DW, Burkman R, Haberman S, Gregory KD, et al. Contemporary patterns of spontaneous labor with normal neonatal outcomes. Obstet Gynecol 2010;116:1281-7.
15. hang J, Troendle J, Mikolajczyk R, Sundaram R, Beaver J,

Fraser W. The natural history of the normal first stage of labor. Obstet Gynecol 2010;115:705-10.
16. Hirmanpour A, Talakoub R, Shafa A, Chitsaz N. Evaluating the Effect of Intrathecal Sufentanil and Meperidine on Shivering after Caesarean Section Under Spinal Anesthesia. Arch Anesth Crit Care 2017;3:365-72.
17. Ching Wong SS, Cheung CW. Analgesic Efficacy and Adverse Effects of Meperidine in Managing Postoperative or Labor Pain: A Narrative Review of Randomized Controlled Trials. Pain Physician 2020;23:175-201.
18. Edwards N, Hartley M, Clyburn P, Harmer M. Epidural pethidine and bupivacaine in labour. Anaesthesia 1992;47:435-7.
19. Ngan Kee WD Ngan Kee WD. Epidural pethidine: pharmacology and clinical experience. Anaesth Intensive Care 1998;26:247-55.
20. Kamranmanesh MR, Aghamohammadi H, Jafari A, Amini Y, Gharaei B. Effect of Intravenous Meperidine in Controlling Post Dural Puncture Headache. Arch Anesth Crit Care 2016;2:189-92.
21. Hashemian F, Farahani F, Sanatkar M. Changes in growth pattern after adenotonsillectomy in children under 12 years old. Acta Med Iran 2010;48:316-9.
22. Chu A, Ma S, Datta S. Analgesia in labour and delivery. Obstet Gynaecol Reprod Med 2017;27:184-90.
23. Brownridge P, RCOG DO. Epidural Bupivaeaine-Pethidine Mixture Clinical Experience Using a Low- dose Combination in Labour. Aust N Z J Obstet Gynaecol 1988;28:17-24.
24. Sengodan SS, Sharona D. Labour analgesia and obstetric outcome in heart disease complicating pregnancy in tertiary care center. Int J Reprod Contracept Obstet Gynecol 2020;9:1235.
25. Alansary AM, Elbeialy MAK. Dexmedetomidine versus fentanyl added to bupivacaine for epidural analgesia in combination with general anesthesia for elective lumbar disc operations: A prospective, randomized double-blinded study. Saudi J Anaesth 2019;13:119-25.
26. Kafshdooz L, Kahroba H, Kafshdooz T, Roghayeh Sheervalilou, Pourfathi H. Labour analgesia; Molecular pathway and the role of nanocarriers: a systematic review. Artif Cells Nanomed Biotechnol 2019;47:927-32.
27. Kocarev M, Khalid F, Khatoon F, Fernando R. Neuraxial labor analgesia: a focused narrative review of the 2017 literature. Curr Opin Anaesthesiol 2018;31:251-7.
28. Cao J, Du Y, Wang YJ, Wu B, Jia J, Wei ZW, et al. Pharmacokinetics of meperidine (pethidine) in rabbit oral fluid: correlation with plasma concentrations after controlled administration. Pharmazie 2018;73:324-8.
29. Hamamoto-Hardman BD, Steffey EP, McKemie DS, Kass PH, Knych HK. Meperidine pharmacokinetics and effects on physiologic parameters and thermal threshold following intravenous administration of three doses to horses. BMC Vet Res 2020;16:368.
30. Qian M, Gao F, Liu J, Xu P. Dexmedetomidine versus fentanyl as adjuvants to ropivacaine for epidural anaesthesia: A systematic review and meta-analysis. Int J Clin Pract 2021;75:e13772.